REMARKS

In the Office Action dated November 8, 2007, the Examiner rejected all of the pending claims as anticipated by Tuschl (WO 02/44321 A1) and invalid under 35 U.S.C. § 112. Applicants respectfully submit that the Examiner misapplied the novelty standard and that when the pending claims as amended are reviewed under the appropriate standard, they should be deemed patentable over the art of record. Applicants also traverse the rejection under section 112.

The Pending Claims and Applicants' Invention

The pending claims are directed to new and non-obvious methods for obtaining siRNA molecules and methods for selecting siRNA sequences. Through the use of these methods one can obtain a particular siRNA that is more likely to be functional than an siRNA sequence that is selected at random or an siRNA molecule that is obtained at random.

Applicants have amended the claim set as follows:

- Claims 1, 43, 61, 68, and 86 have been amended to recite that step (d) is performed after step (c), and step (e) is performed after step (d). Support for these amendments may, for example, be found in: par. [0014] (selecting according to an algorithm); par. [0068] (same); par. [0088] (same); Example III, pars. [0291] – [0299] (first identifying sequences by applying criteria through computer BLAST search, then selecting sequences and synthesizing sequences for use in siRNA gene silencing); Example V, pars. [0302] – [0306] (selecting target, then through the algorithm, applying criteria, then selecting sequence and generating the results in computer readable form and synthesizing sequences); Example VII, pars. [0308] – [0309] (applying formula VII to target genes of ncbi database, generating top 80 –100 sequences that produce highest scores and outputting them in computer readable form).

- Claims 61 and 68 have been amended to remove the phrase "by at least one of a human."
- Claims 1, 43, 61, 68 and 86 have been amended to recite that the criteria are applied through a computer algorithm. Support for these amendments may for example be found in par. [0166] (use of invention with computer algorithm and automatically outputting the optimal siRNA); par. [0217] (computer program to evaluate the criteria and to provide a report ranking); par. [0308] (describing generation of tables through use of computer programs).
- Claims 67 and 69 have been canceled.
- Claims 88 and 89 have been added, which recite that within the duplexes there is 100% complementarity between the sense and antisense regions or sense and antisense sequences.
- Claims 90 and 91 have been added, which recite that the sense and antisense regions or sense and antisense sequence are 19 bases in length.

Through these amendments Applicants have specified the order of the recited steps (c) – (e) in each of the independent claims, and indicated that the methods use computer algorithms.

Thus, each independent claim requires an affirmative step of applying one or more specific criteria through the use of a computer algorithm, then selecting a candidate based on those criteria and either synthesizing the siRNA molecule or outputting an siRNA sequence. (See *e.g.,* claims 1, 43, 68, 61, and 86, step (c) – (e)). Applicants reemphasize that they do not herein claim all compositions that satisfy the recited criteria. Instead, they claim methods in which one affirmatively applies, selects and either synthesizes or outputs based on the application of the criteria. This is a new and more efficient method of reaching a result in which prior to ever testing an siRNA one would select it for gene silencing. By applying the recited criteria before selecting an siRNA one increases the likelihood of selecting a functional siRNA without resorting to trial and error.

Response to Rejection Under 35 U.S.C. § 102(a)

The Examiner maintains her rejection of the claims over Tuschl. For at least the reasons provided below, Applicants respectfully traverse this rejection.

As Applicants previously noted: "Cases involving novelty, with its strict identity requirement, are quite rare." *Trintec v. Top-U.S.A.,* 295 F.3d 1292, 1297 (Fed. Cir. 2002). A rejection under 35 U.S.C. § 102(a) is appropriate if and only if a prior art reference discloses all of the limitations of a claim. *In re Cruciferous Sprout,* 301 F.3d 1343, (Fed. Cir. 2002), *cert. denied,* 538 U.S. 907 (2003); *In re King,* 801 F.2d 1324, 1326 (Fed. Cir. 1986) ("It is axiomatic that anticipation of a claim under § 102 can be found only if the prior art reference discloses every element of the claim . . .").

When a method or process is claimed, in order for a claim to have been anticipated, each step of the method or process must be described or embodied in a single reference, *Glaverbel Societe Anonyme v. Northlake Marketing,* 45 F.3d 1550, 1554 (Fed. Cir. 1995), and "it is incumbent upon the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference." *Ex Parte Levy,* 17 U.S.P.Q. 2d. 1461, 1462 (Bd. Pat. App. Int. 1990); see also *Gerhard Gross v. Vincenzo Spitaleri,* 2002 Pat. App. LEXIS 218 (Bd. Pat. Int.) ("We note that the initial burden of presenting a prima facie case of unpatentability on any ground rests with the examiner."). "The absence of even one limitation recited in a claim from a prior art reference is enough to negate anticipation by that reference." *Louisville Bedding Co. v. Pillowtex,* 1997 U.S. Dist. LEXIS 24023 (W.D. Ky. Aug. 19, 1997).

As the Examiner notes, the steps of Tuschl provide a method for optimizing siRNAs comprising selecting a target gene and synthesizing an siRNA with variations in the 3' overhang. These siRNAs are then empirically tested for optimal activity. A side-by-side comparison of the steps of certain limitations of Applicants' independent claims against Tuschl's steps will demonstrate why Applicants' claimed methods are not anticipated by Tuschl. Significant differences between the disclosed methodologies appear in italics.

Applicants' claims	**Tuschl's method**
(a) selecting a target gene	(a) selecting a target gene
(b) identifying a set of siRNA for the target	(b) identifying a set of siRNA for the target
(c) applying a criteria to the siRNA sequences through a computer algorithm	*(c) synthesizing five siRNAs, each displaced by one nucleotide and eight siRNAs each displaced by one nucleotide*
(d) selecting a candidate siRNA after applying the criteria	*(d) measuring interference of the duplexes after synthesis*
(e) outputting the sequence in computer readable form after selecting it in step (d) (claims 1, 43 and 86); or synthesizing the siRNA after selecting it in step (d) (claims 61 and 68)	*(e) selecting based on the silencing effect in vitro*

For at least four reasons, the italicized steps differ both with respect to their content and their order.

First, in step (c) Applicants apply a computer algorithm to a set of siRNA, wherein the computer algorithm comprises at least one of the recited criteria. By contrast, Tuschl does not apply on computer algorithm or any criteria to a set of siRNA. Instead, in the method of 3.2.1 Tuschl conducts a walk of the gene.

Ultimately, Tuschl concludes that a two nucleotide overhang is critical. However, any siRNA can be constructed with a two-nucleotide overhang and Tuschl is silent as to how to select among different siRNAs that have the same size overhang region. Thus, if one of ordinary skill in the art were to follow the teaching of Tuschl, one would also need to empirically test siRNA with different sequences and then select among them. By contrast, Applicants first select among siRNA of different sequences without needing to empirically test their silencing ability before selecting.

Second, in step (d) Applicants' claims direct selecting an siRNA if it meets the applied criteria and after having applied those criteria. By contrast, Tuschl's method from section 3.2.1 (to which the Examiner points) teaches one to use empirical analysis in

order to select among siRNAs of different sequences, and only after synthesis. Nowhere does Tuschl recite Applicants' criteria or suggest their application.

Third, in step (e) of the various claims, Applicants direct either synthesizing the siRNA or generating an output in computer readable form that comprises the selected sequence after having applied and selected based on the recited criteria. By contrast, Tuschl synthesizes his siRNA prior to selecting the optimal one.

Fourth, as the Examiner notes, Tuschl's conclusion is that one should use siRNA with dinucleotide overhangs and the efficiency of the silencing was in part dependent upon the sequence of the duplex. However, nowhere does Tuschl suggest the use of an algorithm that is based upon any particular feature of his more efficient sequences. Thus, the fact that there was variation in the silencing ability of the different sequences of Tuschl does not suggest Applicants' methods that use the computer algorithms with the recited criteria.

The Examiner points to Tuschl's disclosure of certain synthesized siRNA duplex structures as anticipatory of pending claims. Applicants respectfully submit that although the Examiner has cited an example of siRNA that meets certain of the specified criteria, the Examiner has not shown that the reference teaches to apply the recited criteria. For example, the Examiner points to figure 11E as disclosing antisense strands in which the duplexes comprise a structure in which the total number of A or U residues in the first five, the first four and the first two nucleotides is higher than in the last five, the last four and the last two nucleotides. However, assuming that the Examiner is correct, this would not anticipate Applicants' claims because the Examiner has not shown the use of a computer algorithm containing any of these criteria or the step of selection of the siRNA after the application of the criteria, but before testing *in vitro*.

Response to Rejection Under 35 U.S.C. § 112

The Examiner has taken the position that Applicants' prior amendments to the claims to recite the formation of duplex regions of 19-25 or 19-30 base pairs and in step (c) the application of the criteria with the duplex region, is not supported by the specification. Applicants have removed the phrase "within the duplex region" from step (c) of claims 43, 68 and 86. Accordingly, the rejection applies only to claim 1 and 61 and

the claims that depend on them, and for at least the reasons provided below, Applicants respectfully traverse the rejection.

Applicants note that their disclosure repeatedly emphasizes that one may focus on the duplex region. For example, paragraph [0105] recites "a duplex region," which in the context of that paragraph refers to the portion of the siRNA molecule that does not include overhangs. This paragraph indicates that there may be from 18 – 30 base pairs (*i.e.* a duplex region of that length) in addition to any unpaired overhangs. Par. [0118] explicitly define the "duplex region" to include the portion of the duplex with 79% or greater complementarity and to exclude the overhang regions. Thus, the specification provides support for methods that apply criteria to the duplex regions. See also par. [0114] (referring to duplex regions of 27 base pairs); par. [0147] (referring to 18 to 30 base pairs in length, *e.g.,* 19 base pairs); par. [0266] (referring to 18 –30 base pairs, 18-25 base pairs and 19 base pairs).

The Examiner also expresses concern that the term duplex recited in the passages describing the frequency of A/U base pairs, par. [0237] was not intended to be a duplex region. Specifically, she notes that the duplex region might include a region comprising mismatches as overhangs. Applicants submit that when par. [0237] is read in context, the claims comply with 35 U.S.C.§ 112.

As figure 1 and par. [0079] describe, after the siRNA binds to the RISC complex, the siRNA is unwound. The specification emphasizes: "Duplex unwinding has been shown to be crucial for siRNA functionality in vivo," par. [0144], and the frequency is determined by focusing on "each of the five terminal positions of the duplex," par. [0237]. Although the example described in paragraph [0237] focused on a duplex region of 19 base pairs, because the importance of this criteria is the ability of each end of the duplex to be unwound, a person of ordinary skill would appreciate that regardless of the size of the duplex, it is the terminal nucleotides that are part of that duplex region, *i.e.,* have a complementary base. See also par. [0212] ("low internal thermodynamic stability of the duplex at the 5'-antisense (AS)").

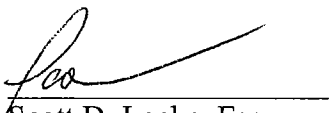
Applicants also respectfully submit that the specification is clear that the substantial complementarity excludes "regions of the polynucleotide strands, such as overhangs, that are selected so as to be noncomplementary" and substantial similarity

excludes "regions of the polynucleotide strands, such as overhangs, that selected so as not to be similar." Par. [0114] Further, paragraph [0118] describes the duplex region in contrast to bases that may exist as 5' and 3' overhangs.

Because overhangs may exist on either the 5' end or the 3'end and the specification is explicit: "they are not included in the calculation of the base pairs," par. [0266] there is a written description of the claim limitation "within a duplex region." For example, if the first or last base on the antisense strand did not have a complementary base on the sense strand, that base on the antisense strand would according to the specification, be an overhang and thus not part of the duplex region. By contrast, if the first two bases of the antisense strand were complementary to the last two nucleotides on the sense strand, but the third nucleotide contained a mismatch, then that third nucleotide would be considered when applying the criteria to the first three, four or five terminal nucleotides with the antisense region of claim 1.

Applicants submit that no fee is necessary with this response other than the fee for Request for Continued Examination. However, if any fee is deemed necessary, Applicants authorize the Patent Office to charge the Deposit Account No. 11-0171 for any such sum.

Respectfully submitted,



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